NANOPARTICLES AND MICROPARTICLES OF NON-LINEAR HYDROPHILIC-HYDROPHOBIC MULTIBLOCK COPOLYMERS

The United States Government has certain rights in this invention by virtue of Grant Number NIH-1R01-GM44884 awarded by the National Institutes of Health.

This invention is in the area of biodegradable block copolymers and nanoparticles and microparticles for the controlled delivery of biologically active material and diagnostic purposes made from the polymers.

BACKGROUND OF THE INVENTION

A major challenge in the area of the parenteral administration of biologically active materials is the development of a controlled delivery device that is small enough for intravenous application and which has a long circulating half-life. Biologically active materials administered in such a controlled fashion into tissue or blood are expected to exhibit decreased toxic side effects compared to when the materials are injected in the form of a solution, and may reduce degradation of sensitive compounds in the plasma.

A number of injectable drug delivery systems have been investigated, including microcapsules, microparticles, liposomes and emulsions. A significant obstacle to the use of these injectable drug delivery materials is the rapid clearance of the materials from the blood stream by the macrophages of the reticuloendothelial system (RES). For example, polystyrene particles as small as sixty nanometers in diameter are cleared from the blood within two to three minutes. By coating these particles with block copolymers based on poly(ethylene glycol) and poly(propylene glycol), their half-lives were significantly increased. L. Illum, S. S. Davis, "The organ uptake of intravenously administered colloidal particles can be altered by using a non-ionic surfactant (poloxamer 338)", *FEBS Lett.,* 167, 79 (1984).

Liposomal drug delivery systems have been extensively considered for the intravenous administration of biologically active materials, because they were expected to freely circulate in the blood. It was found, however, that liposomes are quickly cleared from the blood by uptake through the reticuloendothelial system. The coating of liposomes with poly(ethylene glycol) increases their half life substantially. The flexible and relatively hydrophilic PEG chains apparently induce a stearic effect at the surface of the liposome that reduces protein adsorption and thus RES uptake. T. M. Allen, C. Hansen, *Biochimica et Biophysica Acta,* 1068, 133–141 (1991); T. M. Allen, et al., *Biochimica et Biophysica Acta,* 1066, 29–36 (1991); V. Torchilin, A. Klibanov, "The Antibody-linked Chelating Polymers for Nuclear Therapy and Diagnostics", *Critical Reviews in Therapeutic Drug Carrier Systems,* 7(4), 275–307 (1991); K. Maruyama, et al., *Chem. Pharm. Bull.,* 39(6), 1620–1622 (1991); M. C. Woodle, et al., *Biochimica et Biophysica Acta;* 193–200 (1992); and D. D. Lassic, et al., *Biochimica et Biophysica Acta,* 1070, 187–192 (1991); and A. Klibanov, et al., *Biochimica et Biophysica Acta,* 1062, 142–148 (1991).

European Patent Application Nos. 0 520 888 A1 and 0 520 889 A1 disclose nanoparticles made from linear block copolymer of polylactic acid and poly(ethylene glycol) for the controlled administration of biologically active materials. The applications do not disclose how to modify the copolymer to vary the profile of drug release or how modifying the copolymer would affect distribution and clearance of the delivery devices in vivo. The applications also do not teach how to prepare nanoparticles that are targeted to specific cells or organs, or how to prepare nanospheres that are useful for gamma-imaging for diagnostic purposes.

In U.S. Ser. No. 08/690,370 filed Jul. 23, 1993, injectable particles are described which are formed of a biodegradable solid core containing a biologically active material and poly(alkylene glycol) moieties on the surface or of block copolymers of the poly(alkylene glycol) moieties with biodegradable polymers, which exhibit increased resistance to uptake by the reticuloendothelial system.

It would be desirable to have other types of particles for the controlled delivery of materials that are not rapidly cleared from the blood stream by the macrophages of the reticuloendothelial system, and that can be modified as necessary to target specific cells or organs or manipulate the rate of delivery of the material.

It is an object of the present invention to provide copolymers for preparing microparticles or nanoparticles or coatings which decrease uptake by the reticuloendothelial system and are readily derivatized.

It is another object of the present invention to provide particles for the controlled delivery of diagnostic and therapeutic materials that are not rapidly cleared from the blood stream.

It is another object of the present invention to provide microparticles or nanoparticles that can be modified as necessary to target specific cells or organs or manipulate the rate of delivery of the material.

It is another object of the present invention to provide biodegradable microparticles or nanoparticles that contain detectable materials for diagnostic imaging.

SUMMARY OF THE INVENTION

Non-linear multiblock copolymers are prepared by covalently linking a multifunctional compound with one or more hydrophilic polymers and one or more hydrophobic bioerodible polymers to form a polymer including at least three polymeric blocks. In one embodiment, one or more hydrophilic polymers, such as polyethylene glycol (PEG) chains or polysaccharide moieties, are covalently attached to a multifunctional molecule such as citric acid or tartaric acid, leaving one or more active hydroxyl, carboxylic acid or other reactive functional groups available to attach the hydrophobic polymer(s). The hydrophobic polymer, such as polylactic acid (PLA), polyglycolic acid (PGA), polyanhydrides, polyphosphazenes or polycaprolactone (PCL), is then covalently linked to the multifunctional compound via an appropriate reaction such as ring opening or condensation polymerization. In one embodiment, the multiblock copolymers can have several short PEG chains, for example, with a molecular weight less than 1000, attached to the multifunctional compound. Ligands can be attached to one or more polymer chains to achieve a variety of properties for a wide range of applications.

The block copolymers are useful in forming coatings on implantable devices and, in the most preferred embodiment, nanoparticles and microparticles that are not rapidly cleared from the blood stream by the macrophages of the reticuloendothelial system, and that can be modified as necessary to achieve variable release rates or to target specific cells or organs as desired. The particles can incorporate within or on their surface a substance to be delivered for either therapeutic or diagnostic purposes. In a preferred embodiment, the hydrophilic polymer is a poly(alkylene glycol) (PAG). The terminal hydroxyl group of the poly(alkylene glycol) or